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STUDIES IN THE CHEMISTRY OF CHROMONE EPOXIDES

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Abstract—Chromones and isoflavones, but not flavones, were epoxidized by alkaline hydrogen peroxide. 3-Substituted chromone epoxides were considerably more stable than others; one isoflavone epoxide was converted into a fluorohydrin, another into a 1,2-diol. The latter is a 2-hydroxychromanone and a similarly structured compound was obtained by the cyclisation of 2'-benzoyloxy-2,2-dibromoacetophenone. Acid-catalysed ring-opening of chromone epoxides occurred regioselectively yielding 3-hydroxychromanones. Base-catalysed ring-opening also occurred regioselectively but at the 3-position. Acid- and base-catalysed hydrolysis of 2-methylisoflavone epoxide resulted in cleavage of both heterocyclic rings, yielding, respectively, a 1,3- and a 1,2-diketone. This epoxide formed a cyclic sulphate with sulphuric acid.

The synthesis of chromone epoxides (**2**), by the base-catalysed rearrangement of *secondary* halogeno *α-bromo-o*-acyl(aroyl)oxyacetophenones (**1**) with elimination of hydrogen bromide, has been reported[1] recently. It has now been observed that many chromone epoxides can be synthesised directly by the epoxidation of chromones with alkaline hydrogen peroxide. That process will be described here, together with a study of some of the reactions of these epoxides.

Chromone (**3**) reacted with alkaline hydrogen peroxide to give chromone epoxide (**4**) which was sufficiently stable to be chromatographed on silica gel but not to be crystallised from hydroxylic solvents. With ethanol containing a trace of *p*-toluenesulphonic acid (PTSA), the epoxide **4** formed *trans*-2-ethoxy-3-hydroxychromanone (**5**). The stereochemical assignment is based on a value of 10 Hz for $J_{2,3}$ which is typical[2] and unambiguous for such protons. In contrast, neither flavone (**6**, R = H) nor the two electronically contrasting flavones, 4'-methoxyflavone (**6**, R = OMe) and 4'-nitroflavone (**6**, R = NO_2), showed any reactivity with hydrogen peroxide or *m*-chloro-perbenzoic acid.

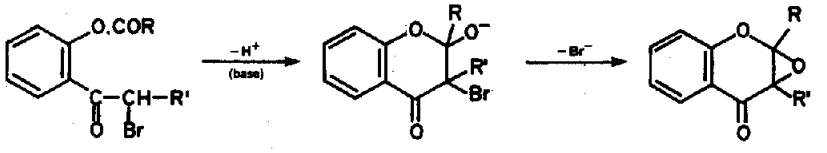
The complete conversion of 2-methylchromone into its epoxide (**7**) by alkaline hydrogen peroxide was found not to be possible as, under the conditions of its formation, the epoxide partially rearranged to 2-methylchromonol (**10**), presumably *via* a 2,3-diol (**8**). The epoxidation, therefore, was usually interrupted before chromonol formation could be observed. It was not possible to separate the epoxide from its precursor without it again rearranging to 2-methylchromonol. Consequently, its reactions were studied mixed with 2-methylchromone.

Unlike the previously reported[1] reaction of a 3-substituted 2-methylchromone epoxide (**11**) which rearranged to a 3-hydroxy-2-methylenechromanone (**12**), 2-methylchromone epoxide (**7**) underwent acid-catalysed rearrangement with PTSA in benzene to form 2-methylchromonol (**10**); the intermediate cation, represented by **9**, eliminating a proton from the 3-position rather than from the 2-Me substituent. The same product was obtained with trichloroacetic acid in benzene. With PTSA in ethanol, the epoxide (**7**) gave a diastereomer of 2-ethoxy-3-hydroxy-2-methylchromanone (**13**). By analogy with simple chromone epoxide (**4**), it is assumed that this product results from the common *anti* addition to epoxides. 2-Methylchromone epoxide (**7**) did not form a fluorohydrin on reaction with boron trifluoroetherate in benzene; it simply rearranged to 2-methylchromonol (**10**). Its reaction with sodium ethoxide gave 3-ethoxy-2-methylchromone (**14**) and confirmed that the above-mentioned base-catalysed ring-opening occurs at the 3-position.

Epoxidation of 7-methoxyisoflavone gave an isoflavone epoxide (**15**) which was considerably more stable than the chromone epoxides lacking a 3-substituent. When heated with ethanol and PTSA, the epoxide yielded a diastereomer of 2-ethoxy-3-hydroxy-7-methoxyisoflavone (**16**), assumed to be that resulting from *anti* addition to the oxirane. Treatment of the epoxide (**15**) with trichloroacetic acid and then with ethanolic potassium hydroxide gave the 1,2-diol, 2,3-dihydroxy-7-methoxy-isoflavanone (**17**). It is of interest[3] that the diol was isolated as the hemiacetal (**17**) and not as the ring-opened form **18**. The possibility of such tautomerism, however, complicates the assignment of the stereochemistry of the diol **17**.

2-Methylisoflavone reacted with alkaline hydrogen peroxide to give 2-methylisoflavone epoxide (**21**), identical with that previously obtained[1] by the cyclisation of a secondary halogeno α-bromo-*o*-acyloxyacetophenone and so confirming the epoxide nature of the products of the α-bromoacetophenone syntheses.[1] The epoxide **21** reacted with boron trifluoride etherate in benzene and gave the fluorohydrin, 2-fluoro-3-hydroxy-2-methylisoflavanone (**20**)—in contrast to the reaction of the 3-unsubstituted epoxide (**7**) of 2-methylchromone. No change of product was observed using dichloromethane as solvent.[4] 2-Methylisoflavone epoxide (**21**), when treated with sulphuric acid in acetic anhydride,[5] yielded the cyclic sulphate with a novel ring-system, 2-methyl-2,3-sulphonyldioxyisoflavanone (**19**).

Treatment of 2-methylisoflavone epoxide (**21**) with trichloroacetic acid in benzene, followed by reaction with aqueous ethanolic potassium hydroxide, gave the diketone, 2-hydroxy-1-(2-hydroxyphenyl)-2-phenyl-1,3-butanedione (**22**). This is the ring-opened tautomer of the diol (**23**) whose analogue (**17**) was obtained from 7-methoxyisoflavone epoxide (**15**). The formation of some 3-hydroxy-2-methyleneisoflavanone (**12**) in the first (acid-catalysed) stage of the reaction was observed. Another reaction which might have yielded the diol (**23**) but which also went a further stage, was that of 2-methylisoflavone



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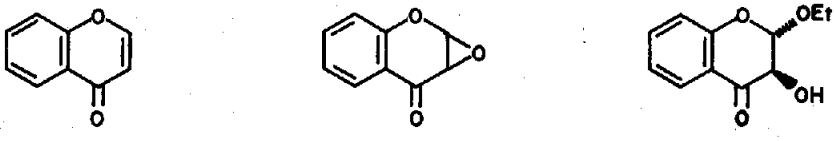

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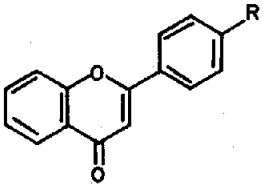

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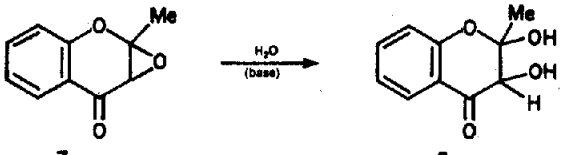

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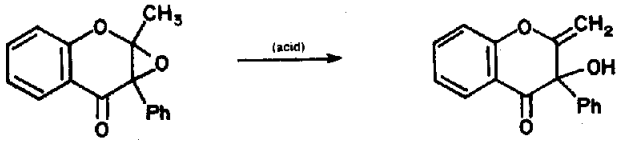

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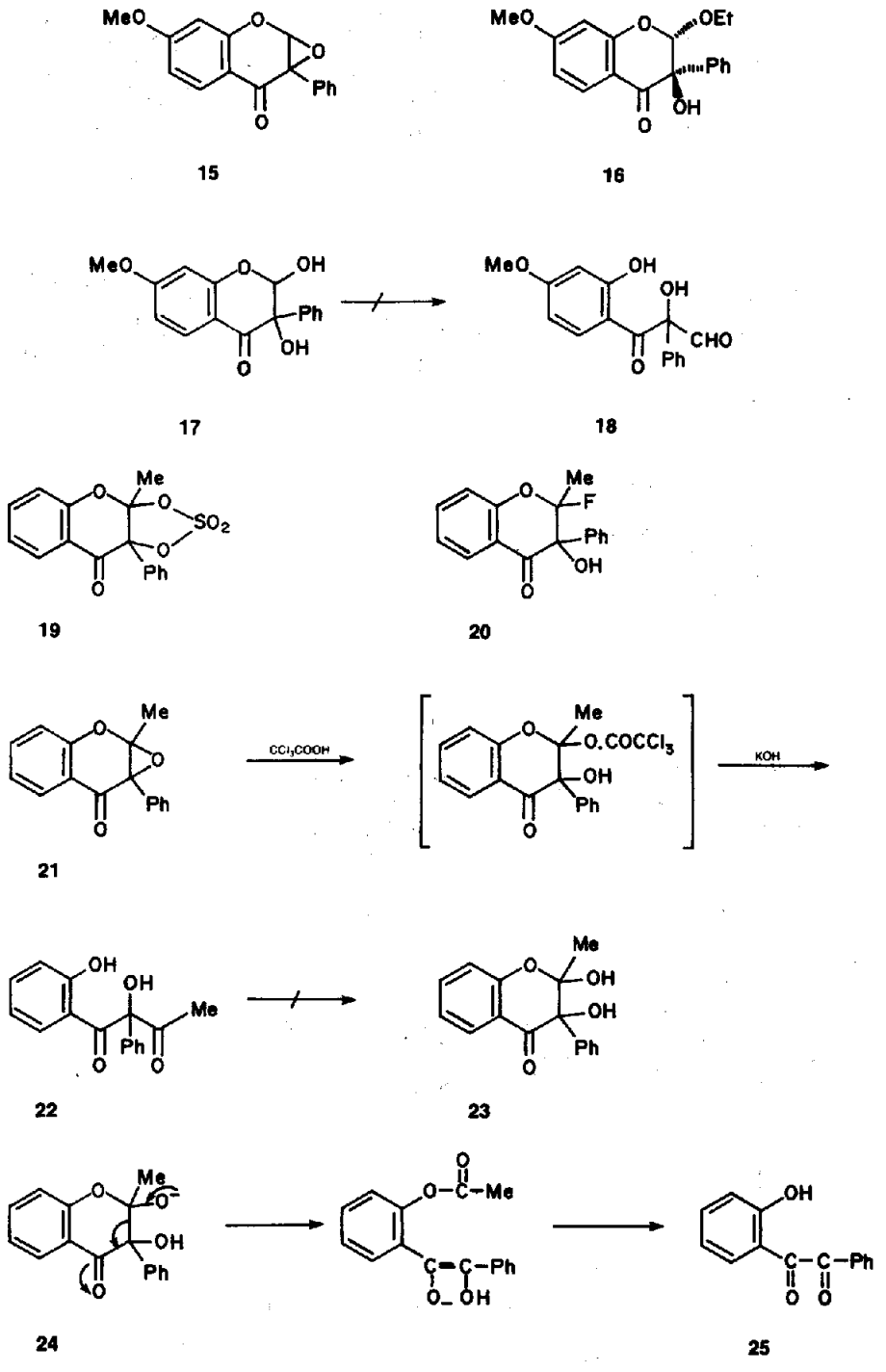
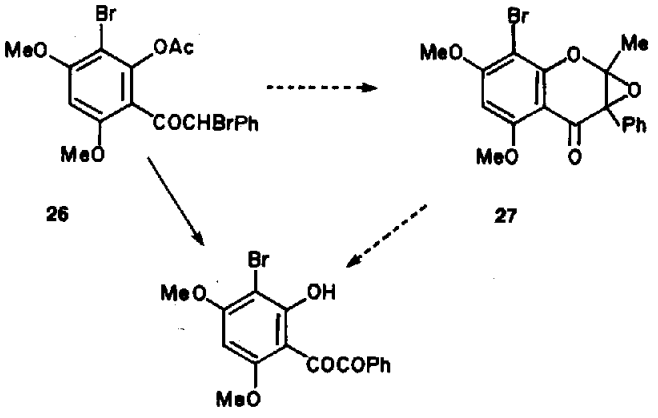


epoxide (**21**) with potassium hydroxide in dimethylsulphoxide. The product obtained was 2-hydroxybenzil (**25**). It is presumed that the heterocyclic ring of the conjugate base (**24**) of the diol, formed by hydroxide attack at the 3-position of the epoxide, fragmented to give the readily hydrolysable acetate of 2-hydroxybenzil (**25**). It has been reported[6] that the attempted formation of another 2-methyl-3-phenylchromone epoxide, 8-bromo-5,7-dimethoxy-2-methylisoflavone epoxide (**27**), by the reaction of 2'-acetoxy-2,3'-dibromo-4',6'-dimethoxy-2-phenylacetophenone (**26**) with methanolic sodium hydroxide, yielded a 2-hydroxybenzil (**28**). It was considered that the benzil arose from hydrolysis of the acetate (**26**), hydroxide substitution of the α-bromine, and subsequent oxidation of the resulting α-ketol. In view of the present result, however, the expected chromone epoxide (**27**) formation may have occurred, to be followed by further reaction with base yielding the benzil (**28**).

An attempt to synthesise 2-cyclopropylisoflavone epoxide (**31**), the acid-catalysed rearrangement of which would be of interest because of the probable intermediacy of a cyclopropylcarbinyl cation, failed. 2'-Hydroxy-2-phenylacetophenone was esterified by



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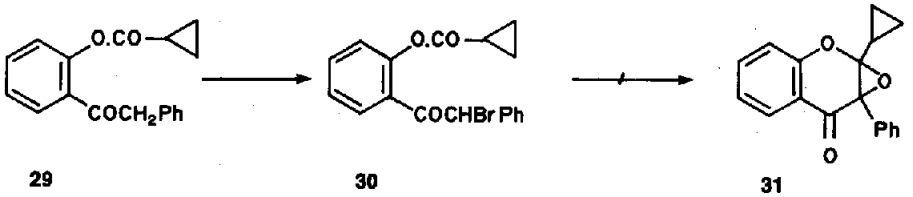

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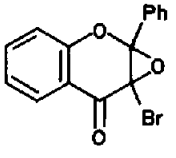

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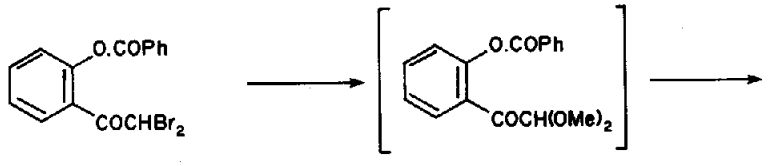

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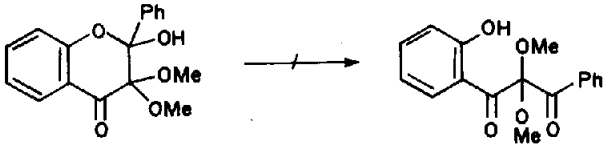

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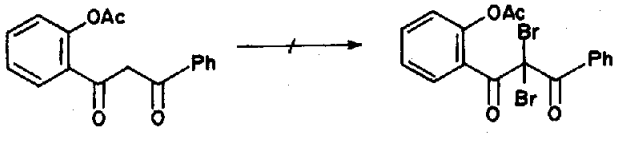

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Table 1. Epoxidation of chromones

Substrate	Reagents	Solvent	Product[a]	M.p.
Chromone (0.23 g)	Aq.H_2O_2 (0.6 ml; 30% w/v)[b]	Me_2CO	Chromone epoxide (4) (0.1 g)	65-6°
	Aq.NaOH (1 ml; 10%)	(15ml)		(n-C_6H_{14})
2-Methylchromone (0.5 g)	Aq.H_2O_2 (1.8 ml; 6% w/v)[c]	Me_2CO	Substrate	
	Aq.NaOH (1.3ml; 10%)	(25 ml)	2-Methylchromone epoxide (7)	
7-Methoxyisoflavone (1.53g)	Aq.H_2O_2 (4.5 ml; 30% w/v)[d]	Me_2CO	7-Methoxyisoflavone epoxide (15)	123-4°
	Aq.NaOH (9 ml; 10%)	(90 ml)	(1.50 g)	(EtOH-H_2O)
2-Methylisoflavone (0.5g)	Aq.H_2O_2 (1.2 ml; 6% w/v)[d]	MeOH	2-Methylisoflavone epoxide[6] (21)	98-9°
	Aq.NaOH (0.9 ml; 10%)	(25 ml)	(0.319 g)	(n-C_6H_{14})

[a] When the work-up of a reaction involved extracting with a solvent, the extract was washed, dried, and evaporated to dryness. The residue was fractionated by t.l.c.

[b] After 18 h. at 0°, the reaction mixture was diluted with water and extracted with chloroform.

[c] After 15 h. at 0°, the reaction mixture was poured into water (100ml) and extracted with diethylether. The residue (0.331g) after the usual work-up, was estimated by integration of the methyl signals of its ^{1}H n.m.r. spectrum to contain substrate and epoxide in the proportions 37:20. This mixture could not be further purified without decomposition of the epoxide.

[d] After 1.5 h. the reaction mixture was diluted with water. The precipitate was collected and crystallized.

Table 2. Reactions of epoxides

Substrate	Reagent	Solvent	Product[a]	M.p.
Chromone epoxide (4) (0.22g)	PTSA[b] (trace)	EtOH (20 ml)	trans-2-Ethoxy-3-hydroxy-chromanone (5)	83-5°
2-Methylchromone epoxide[c] (7)	PTSA[f] (trace)	C_6H_6 (25 ml)	2-Methylchromonol (10) (41 mg)	182-3°
2-Methylchromone epoxide[d] (7)	CCl_3CO_2H in C_6H_6[e] (5 ml; 1 M)	C_6H_6 (10 ml)	2-Methylchromonol (10) (45 mg)	182-3°
2-Methylchromone epoxide[d] (7)	BF_3OEt_2[f] (1 ml)	C_6H_6 (20ml)	2-Methylchromonol (10) (0.122 g)	182-3°
2-Methylchromone epoxide[c] (7)	PTSA[e] (trace)	EtOH (10 ml)	r-2-Ethoxy-t-3-hydroxy-2-methylchromanone (13) (55 mg)	77-9° (n-C_6H_{14})
2-Methylchromone epoxide[d] (7)	NaOEt in EtOH[e] (2ml; 1 M)	EtOH (10 ml)	3-Ethoxy-2-methylchromone (14) (61 mg)	Oil
7-Methoxyisoflavone epoxide (15) (0.2 g)	PTSA[n] (trace)	EtOH (20 ml)	r-2-Ethoxy-t-3-hydroxy-7-methoxy-isoflavanone (16)(0.109g)	120-1° (EtOH-H_2O)
7-Methoxyisoflavone epoxide (15) (0.5 g)	(i) CCl_3COOH[g] (0.67 g) (ii) KOH in EtOH (2 ml; 0.2 M)	C_6H_6 (25 ml) EtOH (30 ml)	2,3-Dihydroxy-7-methoxyiso-flavanone (17) (0.28 g)	125-7° (Et_2O)
2-Methylisoflavone epoxide (21) (0.2 g)	$BF_3.OEt_2$[h] (0.112 g)	C_6H_6 (20 ml)	2-Fluoro-3-hydroxy-2-methyl-isoflavanone (20) (0.115 g)	80-1° (n-C_6H_{14})
2-Methylisoflavone epoxide (21) (0.5 g)	$BF_3.OEt_2$[i] (0.28 g)	CH_2Cl_2 (20 ml)	2-Fluoro-3-hydroxy-2-methyl-isoflavanone (20) (0.452 g)	80-1°

2-Methylisoflavone epoxide (21) (0.5 g)	H_2SO_4[j] (0.201 g)	Ac_2O (10 ml)	2-Methyl-2,3-sulphonyldioxy-isoflavanone (19) (0.145 g)	90-1° ($CHCl_3$-n-C_6H_{14})
2-Methylisoflavone epoxide (21) (0,5 g)	(i) CCl_3CO_2H[k]	C_6H_6 (20 ml)	3-Hydroxy-2-methyleneiso-flavanone[6] (12) (0.14 g)	149-150°
	(ii) KOH in H_2O[l]	EtOH (10 ml)	2-Hydroxy-1-(2-hydroxyphenyl)-2-phenyl-1,3-butanedione (22) (0.121 g)	104 - 5° (n-C_6H_{14})
2-Methylisoflavone epoxide (21) (0.2 g)	Aq. KOH[m] (10 ml; 2 M)	Me_2SO/H_2O (10 ml/40 ml)	2-Hydroxybenzil (25) (75 mg)	74-5°

[a]When the work-up of a reaction involved extracting with a solvent, the extract was washed, dried, and evaporated to dryness. The residue was then fractionated by t.l.c. [b]The reaction mixture was heated for 5 min, diluted with water, and extracted with chloroform. [c]Obtained (see Table I) from 2-methylchromone (0.5 g) and containing about 65% of un-epoxidized chromone. [d]Obtained, as above from 2-methylchromone (1 g). [e]After 0.5 h, the reaction mixture was poured into water and extracted with chloroform. [f]After 0.5 h, the reaction mixture was poured into water and extracted with benzene. [g]The reaction mixture was refluxed for 9 h, washed, dried, and evaporated to dryness. The residue was used in the second stage which was worked-up after 1 h, by diluting with water and extracting with chloroform. [h]After 0.5 h, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with benzene. [i]As above, except that the reaction was carried out at 0° for 30 min; dichloromethane was used for extracting. [j]Stirred at 0° for 10 min. and poured into water. The precipitate was collected and crystallized. [k]In benzene solution (2 ml; 1 M). The reaction mixture was refluxed for 2 h, washed, dried, and evaporated to dryness. The residue was freed of methylene-isoflavone (12) by t.l.c. and the remainder was submitted to the second stage of the reaction. [l]Heated on a steambath for 20 min, diluted with water (50 ml), and extracted with diethyl ether. [m]Heated on a steambath for 4 h, cooled, acidified, and extracted with diethyl ether. [n]Refluxed for 14 h, diluted with water, and extracted with chloro-form.

Table 3. ^{1}H NMR spectroscopic data

Compound	Details of N.m.r. Spectra
(4)	3.77 (d, J 3, 3-H), 5.78 (d, 2-H), 7.09-8.16 (m, Ar).
(5)	1.37 (t, J 7, $-OCH_2\underline{CH_3}$), 3.73 (s, OH), 3.99 (q, $-OCH_2-$), 4.47 (d, J 10, 3-H), 5.23 (d, 2-H), 6.97-8.05 (m, Ar).
(7)	1.91 (s, Me), 3.68 (s, 3-H), 6.98-7.93 (m, Ar).
(13)	1.31 (t, J 7, $-OCH_2\underline{CH_3}$), 1.47 (s, 2-Me), 3.94 (q, $-OCH_2-$), 4.66 (s, OH), 6.97-7.89 (m, Ar).
(14)	1.38 (t, J 7, $-OCH_2\underline{CH_3}$), 2.52 (s, 2-Me), 4.24 (q, $-OCH_2-$), 7.30-8.33 (m, Ar).
(15)	3.92 (s, -OMe), 5.55 (s, 2-H), 6.63-8.06 (m, Ar), 7.52 (s, Ph).
(16)	1.27 (t, J 7, $-OCH_2\underline{CH_3}$), 3.84 (s, -OMe), 3.98 (q, $-OCH_2-$) 4.32 (s, OH), 5.32 (s, 2-H), 6.57-7.94 (m, Ar).
(17)	3.79 (s, -OMe), 4.42-5.04 (s, OH), 6.01 (s, 2-H), 6.49-7.96 (m, Ar).
(19)	1.81 (s, Me), 7.01-8.08 (m, Ar).
(20)	1.69 (d, J 20, Me), 4.26 (s, OH), 7.15-8.05 (m, Ar).
(22)	2.21 (s, Me), 6.70-7.98 (m, Ar), 11.97 (s, ArOH).
(29)	0.89-1.41 (m, $-CH_2CH_2-$), 1.50-2.02 (m, -CH<), 4.26 (s, 2-CH_2-), 7.13-8.16 (m, Ar).
(30)	0.78-1.36 (m, $-CH_2CH_2-$), 1.67-2.13 (m, -CH<), 6.30 (s, 2-CH-), 7.08-8.16 (m, Ar).
(33)	6.71 (s, 2-CH), 7.22-8.44 (m, Ar).
(34)	3.03 (s, -OMe), 3.12 (s, -OMe), 4.83 (s, OH), 7.10-8.20 (m, Ar).
(36)	2.33 (s, Ac), 6.73 (s, 2-CH<), 7.11-8.18 (m, Ar), 16.65 (s, OH).

Table 4. Elemental analysis of new compounds

Compound	Details
(4)	Found: C, 67.0; H, 3.9. $C_9H_6O_3$ requires: C, 66.7; H, 3.7%.
(5)	Found: C, 63.4; H, 5.8. $C_{11}H_{12}O_4$ requires: C, 63.5; H, 5.8%.
(13)	Found: C, 65.2; H, 6.2. $C_{12}H_{14}O_4$ requires: C, 64.9; H, 6.3%.
(14)	Found: C, 70.2; H, 6.2. $C_{12}H_{12}O_3$ requires: C, 70.6; H, 5.9%.
(15)	Found: C, 71.6; H, 4.5. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.5%.
(16)	Found: C, 68.8; H, 6.0. $C_{18}H_{18}O_5$ requires: C, 68.8; H, 5.8%.
(17)	Found: C, 67.4; H, 4.7. $C_{16}H_{14}O_5$ requires: C, 67.1; H, 4.9%.
(19)	Found: C, 57.9; H, 3.8; S, 10.0. $C_{16}H_{12}O_6S$ requires: C, 57.8; H, 3.6, S, 9.6%.
(20)	Found: C, 70.6; H, 4.7; F, 7.0. $C_{16}H_{13}FO_3$ requires: C, 70.6; H, 4.8; F, 7.0%.
(22)	Found: C, 71.1; H, 5.0. $C_{16}H_{14}O_4$ requires: C, 71.1; H, 5.2%.
(29)	Found: C, 77.5; H, 5.5. $C_{18}H_{16}O_3$ requires: C, 77.1; H, 5.8%.
(30)	Found: C, 60.1; H, 4.1; Br, 22.4. $C_{18}H_{15}BrO_3$ requires: C, 60.2; H, 4.2: Br, 22.2%.
(33)	Found: C, 45.6; H, 2.35; Br, 40.3. $C_{15}H_{10}Br_2O_3$ requires: C, 45.3; H, 2.5; Br. 40.2%.
(34)	Found: C, 68.1; H, 5.6. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.4%.
(36)	Found: C, 72.3; H, 5.2. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%.

cyclopropanecarbonyl chloride to give 2'-cyclopropanecarboxy-2-phenylacetophenone (**29**) which, when brominated, gave 2-bromo-2'-cyclopropanecarboxy-2-phenylacetophenone (**30**) but the conditions for cyclizing this ester to the chromone epoxide (**31**), anyway cleanly, were not found.

The syntheses of 3-bromoflavone epoxide (**32**), a possible precursor of flavone epoxide has not been achieved. Dibromination of 2'-benzoyloxyacetophenone gave 2'-benzoyloxy-2,2-dibromoacetophenone (**33**) which, when treated with aqueous methanolic sodium hydroxide, gave 2-hydroxy-3,3-dimethoxyflavanone (**34**) rather than 3-bromoflavone epoxide (**32**). Apparently, both Br atoms were substituted by methoxide before cyclisation occurred. Again, it is of interest[3] that the product was isolated in the hemiketal form (**34**) and not in the 1,3-dione form (**35**). Another approach to the epoxide **32**, *via* 1 - (2 - acetoxyphenyl) - 2,2 - dibromo - 3 - phenyl - 1,3 - propanedione (**37**), failed when the latter (**37**) could not be obtained by the bromination of 1 - (2 - acetoxyphenyl) - 3 - phenyl - 1,3 - propanedione (**36**).

EXPERIMENTAL

^{1}H NMR spectra in $CDCl_3$ with TMS as internal standard were obtained for all products. Chemical shifts are given in ppm (δ), coupling constants in Hz. OH signals were identified by deuteriation. M.ps were taken on a hot-stage apparatus and are uncorrected. Silica gel was used for tlc; products are listed in order of decreasing R_f values.

Table 1 lists the details of the epoxidation reactions and Table 2 the details of epoxidic reactions. Tables 3 and 4 give, respectively, the ^{1}H NMR spectral and elemental analytical details of new compounds.

Cyclopropanecarbonyl chloride (1.5 g) in dry benzene (5 ml) was added dropwise to a soln of 2'-hydroxy-2-phenylacetophenone (3 g) and dry pyridine (1.2 g) in benzene (50 ml). After 2 hr, the mixture was diluted with water (50 ml) and extracted with benzene. The benzene extract was washed, dried, and evaporated to dryness. The residue was fractionated by column chromatography on silica gel and yielded substrate (1.10 g) and *2'-cyclopropane-carboxy-2-phenlyacetophenone* (**29**; 1.35 g), m.p. 110–2° (light petroleum, b.p. 40–60°).

The ester **29** (1.35 g) in AcOH (30 ml) was treated dropwise with Br_2 (0.62 g) in AcOH (5 ml). After 1 hr, the mixture was diluted with water (50 ml) and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried, and evaporated to dryness. The residue, *2-bromo-2'-cyclopropanecarboxy-2-phenyl-acetophenone* (**30**) crystallised from aqueous MeOH in plates (0.93 g), m.p. 96–7°.

Br_2 (3.7 g) in AcOH (15 ml) was added dropwise to a soln of 2'-benzoyloxyacetophenone (2.4 g) in $CHCl_3$ (30 ml). The mixture was washed, dried, and evaporated to dryness, giving *2'-benzoyloxy-2,2-dibromoacetophenone* (**33**; 2.35 g), m.p. 78–9° (aqueous EtOH).

NaOHaq (3.5 ml; 0.5 M) was added to a soln of **33** (0.4 g) in MeOH (15 ml). After 1 hr, the mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried, and evaporated to dryness, giving *2-hydroxy-3,3-dimethoxyflavanone* (**34**; 96 mg), m.p. 106–8° (MeOH).

1-(2-Hydroxyphenyl)-3-phenyl-1,3-propandione (2.4 g) in Ac_2O (20 ml) and pyridine (5 drops) was stirred for 18 hr and poured into water, precipitating *1-(2-acetoxyphenyl)-3-phenyl-1,3-propanedione* (**36**; 2.13 g), m.p. 89–91° (aqueous EtOH).

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